Original Article

Lipocalin-2: Response to a short-term treadmill protocol in obese and normal-weight men

ARSALAN DAMIRCHI[1], FARHAD RAHMANI-NIA[2], JAVAD MEHRABANI[3]

[1]*Associate Professor in Exercise Physiology, University of Guilan, Rasht, Iran*
[2]*Professor in Exercise Physiology, University of Guilan, Rasht, Iran*
[3]*Ph.D Candidate in Exercise Physiology, University of Guilan, Rasht, Iran*

ABSTRACT

Damirchi A, Rahmani-Nia F, Mehrabani J. Lipocalin-2: Response to a short-term treadmill protocol in obese and normal-weight men. *J. Hum. Sport Exerc.* Vol. 6, No. 1, pp. 59-67, 2011. *Background*: Lipocalin-2 (Lcn2) a newer adipocyte-secreted acute phase protein was recently reported to be correlated with potential effects in obesity and inflammation. The reactions of this protein in progressive exercise have not yet been evaluated. *Purpose*: This study was designed to compare of plasma Lcn2 and high-sensitivity C-reactive protein (hs-CRP) levels after participating in a short-term treadmill protocol (STP) in obese and normal-weight men. *Materials and methodology*: In a STP, 9 obese (aged: 43.13±4.6 yrs and BMI: 31.36±1.6 kg/m^2) and 9 normal-weight (aged: 42.88±4.4 yrs and BMI: 23.03±1.7 kg/m^2; mean ± SD) sedentary men that have been selected randomly through volunteers, performed a stepwise maximal aerobic endurance with a treadmill Bruce protocol. *Results*: In prior to STP, Lcn2 level was higher in obese than normal-weight individuals ($p<0.05$). A significant increasing in Lcn2, hs-CRP, and white blood cells (WBC) levels were observed after STP in both of obese and normal-weight groups ($p<0.05$). Also, levels of Lcn2, hs-CRP and WBC were elevated in obese than normal-weight subjects after STP ($p<0.05$). *Conclusion*: It seems Lcn2 and other plasma inflammatory signs were elevated in obese and normal-weight men after participating in one exhaustive short-term exercise. These changes were considerable in obese men. **Key words**: LIPOCALIN 2, VIGOROUS EXERCISE, INFLAMMATION, ADIPOSITY.

Corresponding author. Department of Exercise Physiology, Faculty of Physical Education and Sport Sciences, University of Guilan, Rasht, Iran.
P.O. Box: 41635-1438
E-mail: arsaland388@gmail.com
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INTRODUCTION

Participation in a single bout intense exercise results in an accumulation of inflammatory markers in different tissues (Ciolac and Guimaraes, 2004; Pedersen, 2001). This condition leads to increase of many adipose tissue-derived pro-inflammatory markers containing acute-phase proteins, cytokines, adipokines, and chemokines in circulation (Tataranni et al., 2005; Cancello et al., 2005; Pedersen, 2001). These pro-inflammatory and inflammatory variables are secreted predominantly from enlarged adipocytes and activated macrophages in adipose tissue and liver (Wang et al., 2007; Berggren et al., 2005). The local inflammatory response is accompanied by a systemic reflex known as the acute phase response (Petersen and Pedersen, 2005).

Lipocalin-2 (Lcn2) has recently been recognized as an adipocyte-drived acute phase protein that is positively correlated with potential effects in obesity and inflammation (Choi et al., 2009; Choi et al., 2008; Zhang et al., 2008; Wang et al., 2007; Cowland et al., 2006). It has been implicated in apoptosis and innate immunity (Wang et al., 2007; Yan et al., 2007; Flo et al., 2004). As an adipokine, circulating Lcn2 level has been reported to be increase in obese humans (Wang et al., 2007) and laboratory animals (Yan et al., 2007) than lean controls. It also has been showing that the plasma level of Lcn2 has a significant association with body mass index (BMI), fasting glucose and hyperinsulinaemia (Wang et al., 2007; Choi et al., 2009; Yan et al., 2007; Summer et al., 2009; Esteve et al., 2009). Circulating levels of this adipokine as an acute phase protein, also, has a strong direct correlation with hs-CRP (VanDam and Hu, 2007), and can be as a marker for acute chronic inflammation (Wang et al., 2007; Ross, 1999).

One of the best strategies for preventing obesity and its associated inflammation is participation in regular physical activity (Petersen, 2007). Although, accomplishing of vigorous exercises, particularly a single bout exhaustive intense activities may be leading to systemic inflammation and acute muscular injuries. It is considerable if participants to be obese and sedentary (VanDam and Hu, 2007; Suzuki et al., 2000). The local response to inflammation due to obesity and tissue injury involves the production of adipokines that are released at the site of inflammation (Petersen and Pedersen, 2005). These conditions lead to increase of the circulating concentrations of inflammatory markers such as hs-CRP (Ross, 1999) and Lcn2 (Wang et al., 2007). It has been demonstrated that plasma levels of cytokines are affected by the mode of exercise. The magnitude of the changes in plasma cytokine levels, also, depends on the duration and intensity of exercise (Pedersen, 2001). As reviewed by different studies, there are large increases in plasma pro-inflammatory cytokines during and after a vigorous prolonged endurance exercise (Suzuki, 2000; Suzuki, 2002; Pedersen, 2001). Lcn2 may be, also, plays a role in the inflammation due to acute vigorous exercises (VanDam and Hu, 2007). Whereas, regular physical exercise has beneficial results on obesity and inflammation (Choi et al., 2009), data on acute phase response of Lcn2 to vigorous exhaustive exercise have not yet been investigated. Choi et al. (2009), in an only available study, isn't reported that any changes in Lcn2 level in obese women after 12 weeks moderate exercise training (Choi et al., 2009). In the present study, we want to evaluate this effect in sedentary obese and normal-weight men after a short-term treadmill exercise. With this background, we examined the changes of Lcn2 and hs-CRP circulating levels and insulin resistance index before and after an acute bout of exhaustive treadmill exercise in obese and normal-weight middle-aged men.

MATERIAL AND METHODS

Subjects

Nine obese (aged: 43.13±4.6 yrs and BMI: 31.36±1.6 kg/m^2; mean ± SD) and 9 normal-weight (aged: 42.88±4.4 yrs and BMI: 23.03±1.7 kg/m^2) sedentary men volunteered to participate in this study. In tune up session (7 days before STP), all subjects were asked to complete a personal health and medical history questionnaire, which served as a screening tool. The subjects were given both verbal and written instructions outlining the protocol and written informed consent was obtained before screening. They were familiarized with the procedures and equipments and walked in different gradients and speeds on the treadmill. We excluded subjects who smoked cigarettes or had cardiovascular disease or bypass surgery, diabetes, chronic kidney or liver disease, or had any other major illness or were taking medication that could have affected the laboratory measure results (Mohebbi et al., 2009). The University of Guilan Ethics Committee approved the protocol, which was fully explained to all subjects. Participants were instructed not to engage in any intense exercise and not to change their diet until the measurement day. At second day (6 days before the experimental protocol), VO_2max was measured via indirect calorimetry by an open-circuit gas-analyzer (Cosmed, Quark b^2, Italy) through a graded exercise.

Experimental protocol and laboratory measurements

In measurement day, height, weight and waist circumference measures were recorded. Body mass index (BMI; kg/m^2), fat mass and lean body mass was assessed by bioelectrical impedance analysis using a Body Composition Analyzer (Inbody 3.0®, Biospace Co Ltd, Seoul, Korea). Systolic and diastolic blood pressures were obtained with an electronic sphygmomanometer (HESTIA Mannheim, Japan) above the left brachial artery after 30 minutes rest in the lied position. After 5 minutes warming up that includes light treadmill jogging and muscle, subjects were performed a graded-exercise treadmill run according to the Bruce routine (Bruce, 1973). Briefly, the seven stages of the method corresponded to progressively greater efforts at treadmill speeds of 2.74, 4.02, 5.47, 6.76, 8.05, 8.85, and 9.65 km/hr, respectively. The treadmill is set up with the stage 1 speed (2.74 km/hr) and grade of slope (10% that increases by 2% per stage) and the subject commences the protocol. While the subjects were running on the treadmill, heart rate was recorded using a telemetric device with monitor (Polar, Kempele, Finland). The STP was terminated when the subjects indicated intolerance or exhaustion to a given running. Perceived exertion was rated according to Borg's scale, by using previously explained thumb signs (Borg, 1982). The exercise was followed by a cool down period of 5 minute at a minimal speed and stretching. To control of diurnal variation, the measurements were done in two sequential mornings from 8:00 am to 10:00 am (Tan et al., 2009).

For blood sample collection, all subjects overnight fasted at least for 12 hours and kept at -80 °C for subsequent assay. Samples were obtained by venipuncture after resting for 45 minutes until the start of STP. Sample collection, also, was performed immediately after STP. The plasma Lcn2 levels was measured in duplicate using an enzyme-linked immunosorbent assay (ELISA) kit (R&D Systems, Minneapolis, MN, USA) with an intra-assay CV of 1·0%. A human hs-CRP ELISA kit (Immunodiagnostik, Bensheim, Germany) was used for measuring hs-CRP with an intra-assay CV of 1·7%. The plasma glucose levels was determined by enzymatic (GOD-PAP, Giucose Oxidase-Amino Antipyrine) colorimetric method (Pars Azmoun, Tehran, Iran) and insulin level was measured by a radioimmunoassay (RIA). WBC count was assessed by a laboratory routine method.

Statistical Analyses

Values were expressed as mean ± standard deviation (SD). Before to after changes of exercise were determined by paired sample t-test and differences between two groups were analyzed by Mann-whitney U

or student t-test. P-values less than 0.05 was considered statistically significant. Data analyses were performed with SPSS program (version 13, SPSS, Inc., Chicago, IL).

RESULTS

Anthropometrics and body composition values are presented in table 1.

Table 1. *Mean values (±SD) of characteristics and physiological parameters in obese and normal-weight subjects.*

	Normal-weight (n = 9)	Obese (n = 9)	p value*
Age (yr)	42.9±4.4	43.2±4.6	0.913
Weight (kg)	69.5±6.2	87.7±10.2	0.002*
BMI (kg/m^2)	23.03±1.7	31.4±1.6	0.0001*
BF (%)	17.8±3.4	24.01±3.2	0.002*
FM (kg)	12.4±2.8	20.8±4.6	0.001*
LBM (kg)	57.1±5.1	65.9±7	0.014*
Waist circumference (cm)	78±3.7	89.8±3.8	0.0001*
WHR	0.82±0.04	0.93±0.03	0.001*
Running time (min:s)	15.57±2.3	12.48±3.2	0.001*
VO_2max (ml. kg^{-1}. min^{-1})	34.1±1.5	31.6±1	0.002*
RHR (b/min)	79±8.4	81±2.3	0.151
SBP (mm Hg)	120.1±12	126.1±14.6	0.386
DBP (mm Hg)	79.8±7.7	80.2±8.8	0.906

*Abbreviations: BMI: body mass index; BF: % body fat; FM: fat mass; LBM: lean body mass; WHR: waist to hip ratio; RHR: rest heart rate; SBP: systolic blood pressure; DBP: diastolic blood pressure; *Significance of student t-test for independent groups.*

The changes of measured blood variables before and after the short-term treadmill exercise is shown in table 2, figures 1 and 2. The data showed that the Lcn2 level was higher in obese (152.4±29.3 µg/l) than normal-weight (141±36.5 µg/l) subjects in primary measurement ($p<0.05$). After STP, Lcn2, hs-CRP, and WBC was increased significantly than the baseline in obese (176.9±30.5 vs. 152.4±29.3 µg/l; 6.6±0.4 vs. 3±0.6 mg/l; 12.6±6.7 vs. 7.9±6.2 1000/micl), and normal-weight (155.7±37.3 vs. 141±36.5 µg/l; 5.7±0.5 vs. 2.9±0.8 mg/l; 11.4±4.5 vs. 8.2±4.2 1000/micl), respectively ($p<0.05$). Also, after STP, Lcn2 levels (176.9±30.5 vs. 155.7±37.3 µg/l) and hs-CRP (6.6±0.4 vs. 5.7±0.5 mg/l) were elevated in obese than normal-weight subjects, respectively ($p<0.05$).

Insulin level was increased in obese (14.8±9.5 vs. 11.8±8.9 mU/l) and normal-weight (13.7±8.2 vs. 12.1±9.1 mU/l) individuals after than before of STP ($p<0.05$).

Table 2. *Mean values (±SD) of blood parameters in obese and normal-weight subjects before and after a short-term treadmill exercise.*

	Normal-weight (n = 9)	Obese (n = 9)
FG (mmol/l)		
Before	5.4±0.6	5.6±0.6
After	4.6±0.5	4.5±0.3
Insulin (mU/l)		
Before	12.1±9.1	11.8±8.9
After	13.7±8.2†	14.8±9.5†
WBC (1000/micl)		
Before	8.2±4.2	7.9±6.2
After	11.4±4.5†	12.6±6.7†
Lcn2 (µg/l)		
Before	141±36.5	152.4±29.3*
After	155.7±37.3†	176.9±30.5*†
hs-CRP (mg/l)		
Before	2.9±0.8	3±0.6
After	5.7±0.5†	6.6±0.4*†
Lactate (mmol/l)		
Before	2.9±0.2	3.1±0.2
After	9.4±1.5†	10.2±0.6†

*Abbrev: FG: fasting glucose; WBC: white blood cells; Lcn2: Lipocalin-2; hs-CRP: high-sensitivity C-reactive protein. Significance of student t-test or Mann Whitney U for independent groups: *p<0.05. Paired significance differences before/after short-term treadmill exercise by t-test: †p<0.05.*

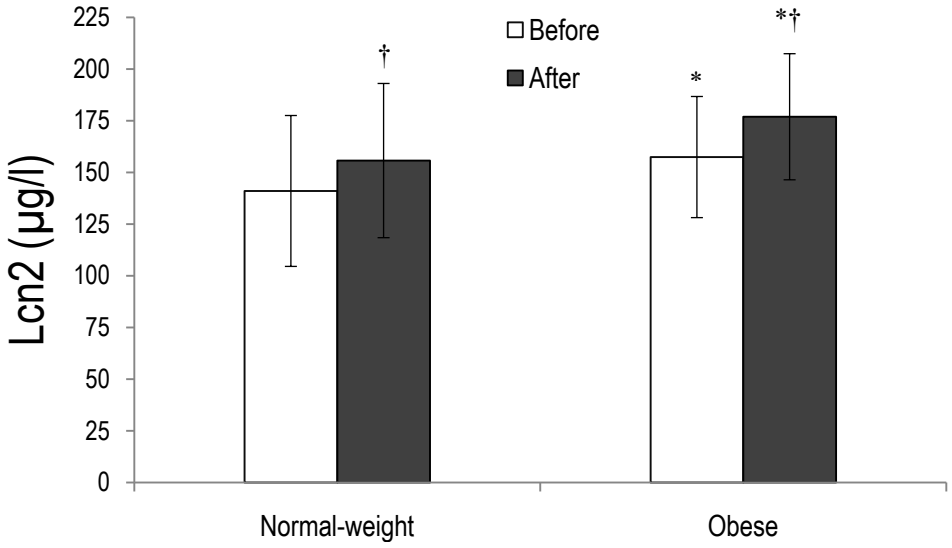

Figure 1. *Mean values (±SD) of Lcn2 in normal-weight (n=9) and obese (n=9) men before and after short-term treadmill protocol. Significance of student t-test or Mann Whitney U for separate groups: *p<0.05. Paired significance differences before/after short-term treadmill protocol by t-test: †p<0.05.*

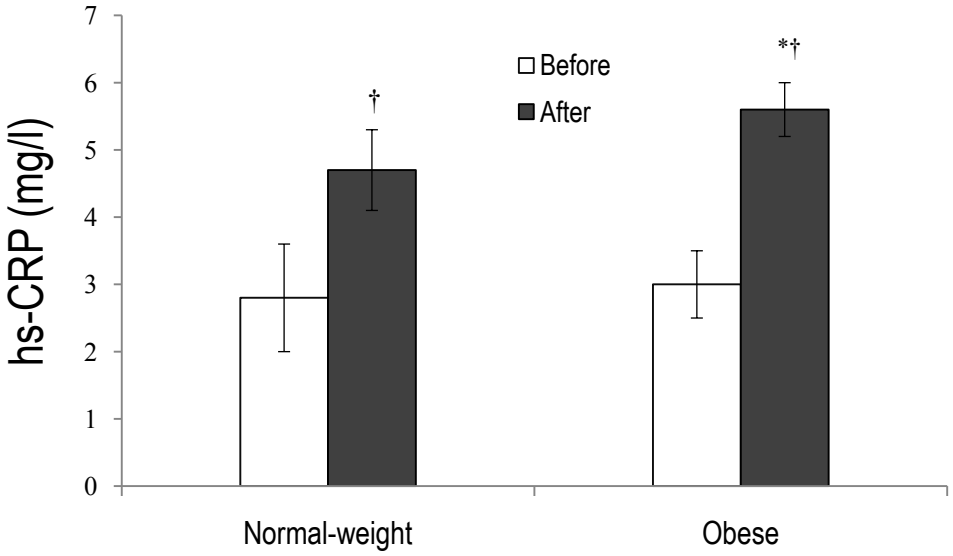

Figure 2. *Mean values (±SD) of hs-CRP in normal-weight (n=9) and obese (n=9) men before and after short-term treadmill exercise. Significance of student t-test or Mann Whitney U for separate groups: *p<0.05. Paired significance differences before/after short-term treadmill exercise by t-test: †p<0.05.*

DISCUSSION

In the present study, we investigated that the effect of a one session intense short-term incremental exercise on the markers that are linked with the incidence of inflammation and cardiovascular diseases in obese and normal-weight adult men. The major findings of present examination were elevated Lcn2, hs-CRP and WBC. Despite Lcn2 has been identified more than one decade, its response to acute exercise training is unknown; although, the effect of longitudinal exercise on Lcn2 has been examined by Choi et al. (2009). They didn't report any changes after exercise training (Choi et al., 2009). Regarding to effect of acute intense exercise, the present study is the first examination about Lcn2. The results showed in obese than normal-weight individuals, like to hs-CRP and WBC levels, Lcn2 concentration was markedly elevated. It seems this difference is probably due to the selective augmentation of its expression in adipocytes and hepatocytes (Law et al., 2010). This increase probably is due to changes of the metabolism process, destruction of muscle cells membrane and elevating of other inflammatory markers such as hs-CRP and WBC. Lcn2 expression is sharply increased after inflammatory stimulation. Expression of Lcn2 in adipose tissue can be induced by lipopolysaccharides, suggesting Lcn2 to be an acute phase protein (Wang et al., 2007). Lcn2 elicits its adverse effects at least partly by stimulating of TNFα, which may in turn magnify the local inflammation and cause impaired energy homeostasis (Law et al., 2010).

Adherent with findings of prior studies (Choi et al., 2009) serum Lcn2 concentrations were found to be higher in obese than lean individuals in the present study. Yan et al. (2007) have been shown this adipocyte-secreted protein influence systemic metabolism and induces insulin resistance. Recently, Wang et al. (2007), showed a higher concentration of Lcn2 in obesity and diabetes. Also, this adipokine is positively related to the BMI, waist circumference and fat percentage, suggesting that the increased fat mass might also account for the elevated blood levels of this adipokine in obese individuals (Wang et al., 2007). We showed a positive relation between Lcn2 level and WC, fat mass and BMI (data isn't shown).

Choi et al. (2009), also, have been demonstrated that Lcn2 can use by researchers and clinicians as the inflammatory index.

The results showed in obese than normal-weight individuals hs-CRP levels was increased after than before STP. WBC and hs-CRP are related with stresses due to high intensity exercises (Mathur and Pedersen, 2008). This finding is not agreement with previous studies (Damirchi et al., 2008; Paczeck et al., 2005). Damirchi et al. (2008) have been demonstrated no significant change in blood level of CRP before and after a single bout of exercise like to Paczeck et al. (2005). Whiles Choi et al. (2009) showed an improving in hs-CRP without significant change in serum Lcn2 levels in adult obese women after 12 weeks moderate exercise. This contradiction in reports can be a perspective to more investigation on Lcn2 and its relationship with other inflammatory markers in acute and chronic exercises. It is nature that the response of Lcn2 to acute exercises did not investigate and need to more studies. According to the findings, it seems the STP-induced acute phase inflammation results in an increase in Lcn2 and hs-CRP levels in both obese and normal-weight participants. Of course, it is reported that a direct relation between the Lcn2 and hs-CRP levels (Choei et al., 2009). It based this reason, increasing of Lcn2 was anticipated. So, Lcn2 can be recognized as an inflammatory marker that increases after a progressive physiological stress in sedentary individuals. Previous studies demonstrate that regular exercise protects of the organism against diseases and complications linked to chronic low grade systemic inflammation (Matur and Pedersen, 2008). Indeed, the majority of studies suggest that regular exercise has anti inflammatory effects; nevertheless, an intense exercise as an inflammatory stimulus induces destruction of protein and adipose tissues. Although, the possibility exists that, with regular exercise, the anti inflammatory effects of an acute bout of exercise will protect against chronic systemic low-grade inflammation and thereby offer protection against insulin complications, but such a link between the acute effects of exercise and the long-term benefits has not yet been proven (Bruunsgaard, 2006; Petersen and Pedersen, 2005).

Increasing if insulin levels after STP, was other findings of this study. Insulin is an important component of that involved in insulin resistance. Response of insulin to acute and chronic exercise might be different. It has been demonstrated that single bout of exercise increases the glucose disposition by the insulin in normal subjects and in obese individuals with insulin resistance (Ciolac and Guimaraes, 2004). These changes may be a reflex of increasing in glucose uptake during exercise. Major portion of energy during exercise running obtain from metabolism of blood glucose. It's clear this action and glucose intake be done by insulin effect (Ciolac and Guimaraes, 2004).

Despite the clear benefit of the regular exercise on the insulin, there are situations in which the acute exercise does not improve the insulin sensibility, and it may even worsen it. The insulin sensibility is decreased after the marathon running as well as after exhausting exercise such as running up in a steep street (Ciolac and Guimaraes, 2004). This discussion is contrast to my finding. We haven't revised the relation between Lcn2 and insulin. For this aim, it needs more population to study.

CONCLUSION

We show for the first time the response of Lcn2 circulation level to an exhaustive short-term exercise in sedentary obese men. The results provide novel insights in blood Lcn2 concentration to a session intense exercise. It seems participation in an exhaustive aerobic exercise can lead to increase of Lcn2 and hs-CRP in sedentary obese men. However, these results need to be further investigated in the future.

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